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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/545,428	04/07/2000	Michel F Levesque M D	CEDAR-044526	1086

7590 11/20/2002

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EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	23

DATE MAILED: 11/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/545,428	LEVESQUE M D ET AL.	
	Examiner	Art Unit	
	Mary M. Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,8,11,12,16 and 21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,8,11,12,16 and 21-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 April 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The restriction requirement made in the previous Office action is moot in view of the amendments to the claims filed Aug. 28, 2002.

Information Disclosure Statement

2. The information disclosure statement filed fails to comply with 37 CFR 1.98(a)(1 and 2) for the European Search Report references 31 and 32. Applicant is requested to submit a list of the references contained within the search reports and copies of the references for further consideration.

Drawings

3. The drawings have been reviewed by an official draftsman and the PTO 948 form is attached.

Specification

4. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means"

and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

5. The abstract of the disclosure is objected to because it is longer than 150 words. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

6.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5, line 4, lacks antecedent basis for "the neurogenic transcription factor NeuroD1...." Since it is unclear from the claim how many different species of NeuroD1 and the other transcription factors there are (ie. from different organisms), the phrase would be more proper if stated, "a neurogenic transcription factor...." Claim 5, line 13, would be more clearly stated if there was a punctuation mark between the words "glial cell" and "said cell".

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 2, 5, 8, 11, 12, 16 and 21-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to an in vitro method of transdifferentiating an epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell comprising:

a) culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s), said cell(s) derived from the skin of a mammalian subject;

b) transferring said epidermal basal cell, in vitro, with one or more eukaryotic expression vector(s) containing at least one cDNA encoding a human neurogenic transcription factor, or homologous non-human counterpart, or active fragment(s) thereof, selected from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, such that at least one of the neurogenic transcription factor(s) is expressed in said cell;

c) growing the transfected cell in the presence of at least one antisense oligonucleotide comprising a segment of a human MSX1 gene and/or human HES1 gene, or homologous non-

human counterpart of either of these, in an amount sufficient to suppress the expression of functional MSX1 gene product and/or HES1 gene product;

d) growing said epidermal cell with a retinoid and at least one signal molecule selected from the group consisting of CNTF, sonic hedgehog, sonic hedgehog aminoterminal peptide, and IK-6, whereby the cell is transdifferentiated into a cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell; and

e) wherein the physiological and/or immunological feature is expression of a marker selected from the group consisting of glial fibrillary acidic protein, and O4, or a combination of these.

Claim 2 is drawn to the method of claim 1, wherein the eukaryotic expression vector(s) of the transfection step comprise a CMV promoter sequence operatively linked to a DNA(s) encoding the neurogenic transcription factor selected from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1.

Claim 5 is drawn to a trandifferentiated cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell comprising:

an epidermal basal cell transfected with one or more eukaryotic expression vectors comprising a CMV promoter sequence operatively linked to a DNA(s) encoding the neurogenic transcription factor, or homologous non-human counterpart, or active fragment(s) thereof, selected from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, wherein the DNA encoding the neurogenic transcription factor is of human origin, or is a non-human

homologous counterpart, or is an active fragment of a gene encoding any of these, said cell being treated with at least one antisense oligonucleotide comprising a segment(s) of human MSX1 gene or human HES1 gene, or non-human homologous counterpart thereof, and wherein said cell was grown in the presence of a retinoid and at least one signal molecule selected from the group consisting of CNTF, IL-6, sonic hedgehog, and sonic hedgehog aminoterminal peptide, thereby transdifferentiating said epidermal basal cell into a cell having one or more morphological, physiological and/or immunological feature(s) of a glial cell said cell expressing at least one marker selected from the group consisting of glial fibrillary acidic protein (GFAP) and O4, or a combination of these.

Claim 8 is drawn to a transdifferentiated cell produced by the process of claim 1.

Claim 11 is drawn to a kit for converting, in vitro, epidermal basal cells into cells having one or more morphological, physiological and/or immunological feature(S) of a glial cell, said kit comprising:

one or more eukaryotic expression vectors containing cDNA encoding a human neurogenic transcription factor, or fragment thereof, from the group consisting of NeuroD1, NeuroD2, ASH1, Zic1, Zic3, and MyT1, or a non-human homologous counterpart of any of these;

at least one antisense oligonucleotide corresponding to the human MSX1 gene, the human HES1 gene, or a non-human homologous \ counterpart of either of these,

and a retinoid and at least one signal molecule selected from the group consisting of CNTF, sonic hedgehog, and sonic hedgehog aminoterminal peptide.

Claim 12 is drawn to the kit of claim 11 further comprising instructions for using (a), (b), and c) in transdifferentiating a mammalian subject's epidermal basal cell(s).

Claim 16 is drawn to the transdifferentiated cell of claim 8, wherein the cell further displays the physiological feature of a lack of mitotic activity under cell culture conditions which induce differentiation in neural progenitor cells.

Claim 22 is drawn to the transdifferentiated cell of claim 8 wherein the cell is of human origin.

Claim 23 is drawn to the cell of claim 8, wherein the transdifferentiated cell has a morphological, physiological, or immunological feature specific to an astroglial or oligodendroglial cell.

Claim 24 is drawn to the transdifferentiated cell of claim 23, wherein the physiological and/or immunological feature is expression of glial fibrillary acidic protein (GFAP) or O4.

Claim 25 is drawn to an in vitro cell culture derived from the transdifferentiated cell of claim 8, comprising a plurality of cells that express one or more morphological, physiological and/or immunological feature(s) of a glial cell.

Claim 26 is drawn to the method of claim 1, wherein culturing a proliferating epidermal basal cell population comprising one or more epidermal basal cell(s) comprises separating basal cells from keratinocytes using a calcium-free medium.

Claim 27 is drawn to the method of claim 1, wherein said antisense oligonucleotide(s) is modified with one or more thio groups.

The specification as filed teaches that human adult skin was cultured and transfected with pRcCMVneo vectors containing B-gal, NeuroD1, NeuroD2, hASH1, Zic1 or hMyT1 human genes. The specification teaches in example 3 the design of two antisense oligonucleotides to target human MSX1 and two antisense oligonucleotides to target human HES1. In example 4, the specification teaches the methods for detection of transdifferentiation of the epidermal cells to neural cells as immunohistochemical detection of neurofilament M, neural specific tubulin, neural specific enolase, microtubule associated protein 2, neurofilaments Mix, filial fibrillary acidic protein, and morphological criteria. The specification teaches that cells with neurites longer than three cell diameters (50 microns or longer) and expressing at least one neuronal marker were counted as neurons. Table 1 teaches the results of the transdifferentiation experiments showing that a combination of neurogenic transcription factor expression coupled with decrease in MSX1 and HES1 expression was most effective at establishing transdifferentiation. The specification as filed does not teach by way of example that any of the obtained cells from the methods disclosed could be considered glial cells. The specification only teaches in Table 1 a defined set of cells having some characteristic of a differentiated neuronal cell, the structure of which is not adequately described therein, and would not appear to have the instantly claimed features of a glial cell. The specification teaches broadly that different characteristics of neuronal cells were evaluated, but does not specify the uniformity of such

characteristics amongst or between the cells having different transcription factors and antisense sequences applied, nor how these neuronal cell characteristics relate to glial cells. Therefore, it is not clear to one of skill in the art that the cells taught as differentiated neuronal cells have the glial structures now claimed or that a representative number of such glial cells was described by the specification as filed to show that applicant indeed had possession of glial cells at the time the invention was made.

The activation of one or several genes in epidermal cells leading to the transcription of one or more neuronal markers or a single physiological response does not indicate that such modified epidermal cells would necessarily have the function of glial cells based on cell acquisition of one or several such morphological features.

The claims drawn to kits containing ingredients for differentiation of epidermal cells to neuronal cells are further not adequately described by the specification as filed because the specification does not teach the structures of the glial cells based on the application of the various kit components.

In summary, the claims are drawn to a genus of transdifferentiated glial cells having different characteristics yet the specification as filed does not teach the correlation of these characteristics to the methods applied for transdifferentiation of the epidermal cells. Therefore, while the cells may suggest specific neuronal features, they do not show possession of a representative number of whole, complete, glial cells to show possession to one of skill in the art of the genus of differentiated glial cells as claimed.

The textbook entitled "The Functional Roles of Glial Cells in Health and Disease", vol. 468 from the Advances in Experimental Medicine and Biology series, Ed. By Rebecca Matsas and Marco Tsacopoulos, Kluwer Academic/Plenum Publishers, New York, NY, 1999, teaches the following about glial cells in the preface: "Glial cells outnumber neurons and make up about one-half of the bulk of the nervous system. They are divided into two major classes: first, the macroglia, which include astrocytes and oligodendrocytes in the central nervous system, and the Schwann cells in the peripheral nervous system; and second, the microglial cells. These different classes of glial cells have different functions and contribute in different ways in the development, function, and the pathology of the nervous system." The complexity of glial cell development, the discovered components of cell differentiation and development, and cell survival as a functioning glial cells are reviewed in chapter 1, Jessen et al., pages 3-10. It is stated on page 4, line 5, that "[l]ittle is known about the mechanisms that regulate the entry of crest cells to the glial lineage. One of the difficulties in studying this first step in PNS glial development has been the lack of a glial differentiation marker that defines an early lineage entry." They further state on page 4 that "[o]ne of the most notable features of the precursor cell is its acute dependence on axonal survival signals." On page 6, they state that "A striking feature of the Schwann cell phenotype is how unstable it is. If a nerve is an adult animal is transected, the myelinating and non-myelinating cells in the distal stump will promptly undergo radical lacerations in morphology and gene expression. The eventual outcome is the generation of an apparently single population of cells that show a state of differentiation comparable to that of immature cells

prior to the formation of myelinating an non-myelinating cells....this process involves the dedifferentiation or development regression of individual Schwann cells and myelin break-down." These teachings provide the complexity in the art for the types of glial cells, their functions, and their carefully regulated cell phenotypes.

While the textbook, Developmental Biology, 5th Ed. , Scott F. Gilbert, Sinauer Associates, Inc. Pub., Sunderland, Mass., 1997, pages 297-299, taught in Figure 7.42, the "Hypothetical lineage restriction in the cells of the quail cephalic neural crest", the potential for glial cell development to take many different paths is clear. Neither the prior art nor the specification as filed taught the clearly delineated pathology of development of any type of glial cell from epidermal basal cells.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species

> by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

In the instant case, the methods of making the claimed glial cells, depend on the transfection of epidermal basal cells with different growth factors, and antisense to inhibit differentiation into epidermal cells. The claims read on administration of whole genes or gene fragment from any species of organism, a representative number of species of which is not provided in the specification as filed. It is not clear from the specification as filed what the structures of the fragments are that would function equivalently to the whole growth factor gene. Further, as pointed out above, there is a high level of unpredictability as to what the cells will look like, and what they will express based on the complexity of the developmental regulation of glial cells. Neither the specification as filed nor the prior art provide sufficient identifying characteristics of the resulting glial cells such that one of skill in the art would be able to visualize the types of glial cells produced from the claimed methods. In fact, the disclosure of the claimed methods in the specification as filed does not provide evidence that glial cells are generated, but rather than neuronal type cells are generated. Absent further description of the exact gĕnes expressed in the epidermal basal cells, and the expected type of glial cells produced, one of skill in the art would not have recognized that applicant was in possession of a

representative number of species of the claimed transdifferentiated glial cells nor methods of making such transdifferentiated glial cells as the time the invention was made.

10. Claims 1, 2, 5, 8, 11, 12, 16 and 21-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

MPEP 2164 teaches the following standards for a determination of whether the specification taught how to make and use the claimed invention at the time the invention was made by weighing whether or not undue experimentation was required to make and use the invention as claimed. MPEP 2164.01(a) lists the factors for determining "whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) the amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)"

See the description of the claims above.

The specification as filed teaches that human adult skin was cultured and transfected with pRcCMVneo vectors containing B-gal, NeuroD1, NeuroD2, hASH1, Zic1 or hMyT1 human genes. The specification teaches in example 3 the design of two antisense oligonucleotides to target human MSX1 and two antisense oligonucleotides to target human HES1. In example 4, the specification teaches the methods for detection of transdifferentiation of the epidermal cells to neural cells as immunohistochemical detection of neurofilament M, neural specific tubulin, neural specific enolase, microtubule associated protein 2, neurofilaments Mix, filial fibrillary acidic protein, and morphological criteria. The specification teaches that cells with neurites longer than three cell diameters (50 microns or longer) and expressing at least one neuronal marker were counted as neurons. Table 1 teaches the results of the transdifferentiation experiments showing that a combination of neurogenic transcription factor expression coupled with decrease in MSX1 and HES1 expression was most effective at establishing transdifferentiation. The specification as filed does not teach by way of example that any of the obtained cells from the methods disclosed could be considered glial cells. The specification only teaches in Table 1 a defined set of cells having some characteristic of a differentiated neuronal cell, the structure of which is not adequately described therein, and would not appear to have the instantly claimed features of a glial cell. The specification teaches broadly that different characteristics of neuronal cells were evaluated, but does not specify the uniformity of such characteristics amongst or between the cells having different transcription factors and antisense sequences applied, nor how these neuronal cell characteristics relate to glial cells. Therefore, it

is not clear to one of skill in the art that the cells taught as differentiated neuronal cells have the glial structures now claimed or that a representative number of such glial cells was described by the specification as filed to show that applicant indeed had possession of glial cells at the time the invention was made.

The activation of one or several genes in epidermal cells leading to the transcription of one or more neuronal markers or a single physiological response does not indicate that such modified epidermal cells would necessarily have the function of glial cells based on cell acquisition of one or several such morphological features.

The claims drawn to kits containing ingredients for differentiation of epidermal cells to neuronal cells are further not enabled by the specification as filed because the specification does not teach the structures of the glial cells based on the application of the various kit components.

The instant claims are drawn to a genus of transdifferentiated glial cells having different characteristics (expression of markers) yet the specification as filed does not teach the correlation of these characteristics to the methods applied for transdifferentiation of the epidermal cells. Therefore, while the cells may suggest specific neuronal features, they do not show possession of a representative number of whole, complete, glial cells to show to one of skill in the art how to make and use the breath of differentiated glial cells claimed.

The textbook entitled "The Functional Roles of Glial Cells in Health and Disease", vol. 468 from the Advances in Experimental Medicine and Biology series, Ed. By Rebecca Matsas and Marco Tsacopoulos, Kluwer Academic/Plenum Publishers, New York, NY, 1999, teaches

the following about glial cells in the preface: "Glial cells outnumber neurons and make up about one-half of the bulk of the nervous system. They are divided into two major classes: first, the macroglia, which include astrocytes and oligodendrocytes in the central nervous system, and the Schwann cells in the peripheral nervous system; and second, the microglial cells. These different classes of glial cells have different functions and contribute in different ways in the development, function, and the pathology of the nervous system." The complexity of glial cell development, the discovered components of cell differentiation and development, and cell survival as a functioning glial cells are reviewed in chapter 1, Jessen et al., pages 3-10. It is stated on page 4, line 5, that "[l]ittle is known about the mechanisms that regulate the entry of crest cells to the glial lineage. One of the difficulties in studying this first step in PNS glial development has been the lack of a glial differentiation marker that defines an early lineage entry." They further state on page 4 that "[o]ne of the most notable features of the precursor cell is its acute dependence on axonal survival signals." On page 6, they state that "A striking feature of the Schwann cell phenotype is how unstable it is. If a nerve is an adult animal is transected, the myelinating and non-myelinating cells in the distal stump will promptly undergo radical lacerations in morphology and gene expression. The eventual outcome is the generation of an apparently single population of cells that show a state of differentiation comparable to that of immature cells prior to the formation of myelinating an non-myelinating cells....this process involves the dedifferentiation or development regression of individual Schwann cells and myelin break-

down." These teachings provide the complexity in the art for the types of glial cells, their functions, and their carefully regulated cell phenotypes.

While the textbook, Developmental Biology, 5th Ed. , Scott F. Gilbert, Sinauer Associates, Inc. Pub., Sunderland, Mass., 1997, pages 297-299, taught in Figure 7.42, the "Hypothetical lineage restriction in the cells of the quail cephalic neural crest", the potential for glial cell development to take many different paths is clear. Neither the prior art nor the specification as filed taught the clearly delineated pathology of development of any type of glial cell from epidermal basal cells.

Thus the level of unpredictability in the field of development of glial cells from epidermal basal cells was high. One of skill in the art could not predict whether or not glial cells could be produced from epidermal basal cells in cell culture. Nor could one of skill in the art predict whether or not glial cells could be made from the methods disclosed in the instant specification as filed. Although applicant has provided a few glial marker proteins, the evidence of expression of these proteins alone, does not clearly teach one of skill in the art that glial cells have been achieved. As argued previously and above, the types of cells taught in the instant specification are defined as neuronal cells based on a few criteria such as morphological extensions, however, such criteria, do not enable one of skill in the art to make and use glial cells. Absent more specific guidance in the art for which genes must be expressed in the epidermal basal cells, under what cell culture conditions, with an expectation of certain concrete indicators of glial cell pathology, one of skill in the art would necessarily practice an undue amount of experimentation

to make and use the breath of claimed transdifferentiated glial cells and methods of making said cells.

11. Claims 1, 2, 5, 8, 11, 12, 16, 22-27 are free of the prior art since the prior art did not teach nor fairly suggest the claimed step of use of antisense to MSX1 and HES1 found in each of the instant method and composition claims.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader* may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
November 18, 2002